Remarks

Further and favorable reconsideration is respectfully requested in view of the foregoing amendments and following remarks.

A spelling error has been corrected on page 6 of the specification.

With regard to the objection to the drawings on page 4 of the Office Action, please see the replacement drawing for Fig. 1 submitted concurrently herewith by separate cover letter.

The abstract has been amended to place it in the form of a single paragraph, in response to the objection to the abstract on page 5 of the Office Action, thus rendering this objection moot. Additional editorial changes have also been made.

Claims 1 and 4 have been amended in response to the rejection under the second paragraph of 35 U.S.C. §112, thus rendering this rejection moot.

Claims 3 and 5 have also been amended to make editorial changes.

New claim 6 has been added to the application, and is the same as claim 1 (but in dependent form) except that claim 6 uses "consists of" language and allows for the possibility of incorporating a softening agent, an absorption promoting agent and a sweeting agent in the drug layer, based on the disclosure at page 7, line 5 to page 8, line 5 of the specification.

The patentability of the presently claimed invention over the disclosures of the references relied upon by the Examiner in rejecting the claims will be apparent upon consideration of the following remarks.

Present Invention

The present invention relates to a patch containing fentanyl for the mucous membrane of the oral cavity, which can be prepared by laminating on one side of a drug layer 1 (which contains fentanyl or its salt as an active ingredient and shows adhesivity due to being dissolved in or swelled with water), a support layer 2 (hardly soluble or insoluble in water), and a backing 3 in this order, and provides a patch which:

(1) does not need any complex procedures when it is applied,

(2) gives only a slightly uncomfortable feeling in the oral cavity,

(3) can quickly increase the serum concentration as the drug is absorbed almost at the applied region,

(4) results in less transfer of the drug into the gastrointestinal tract by preventing drug release into other parts of the oral cavity than the applied region,

(5) is easily torn off when it becomes unnecessary,

(6) can easily control the serum concentration of the drug,

(7) is usable as a rescue preparation for pang during therapy for cancer pain, and

(8) is highly safe.

The present inventors found that a drug layer which contains fentanyl or its salt as an active ingredient, methyl vinyl ether-maleic anhydride copolymer as an adhesive (e.g. 5 to 90 wt/%), and at least one substance selected from the group consisting of hydroxypropyl cellulose, hydroxypropyl methylcellulose and hydroxyethyl cellulose as a thickener (e.g. 0.2 to 80wt/%) shows sufficient adhesivity to the mucous membrane of the oral cavity due to the presence of water therein, and easily releases the drug from the applied surface and quickly increases the serum concentration of fentanyl. Furthermore, by laminating a support layer which is insoluble or hardly soluble in water on the opposite side of the adhesive surface of the drug layer, the drug is hardly swallowed with saliva due to protecting to release the drug into other regions in the oral cavity except the applied region. In addition, by equipping a backing thereto and making the patch thick to some extent, regardless of smallness of size, handling the patch (such as by picking up, applying and tearing off), becomes easy, and a patch containing fentanyl for the mucous membrane of the oral cavity which easily controls the serum concentration can be obtained.

The excellent effects of the present invention are shown in Tests 1 to 4, and Figures 2 to 5, of the application.

Prior Art

The rejection of claim 1 under 35 U.S.C. §102(b) as being anticipated by Theeuwes et al. (US '017) is respectfully traversed.

This reference relates to an iontophoretic delivery device, and therefore, is completely different from the present invention in its technical field.

That is, Theeuwes et al. relates to a device which has a plurality of essentially parallel layers, including (a) a counter electrode layer, (b) a donor electrode layer in electrical contact with the counter electrode layer, and (c) a donor reservoir layer comprising an agent to be

delivered, and having a major surface which is adapted to be placed in agent transmitting relation with the body surface. See column 3, lines 20-27.

The patch of the present invention comprises a support layer, a drug layer containing an adhesive, and a backing, and is different from the device disclosed in Theeuwes et al. Furthermore, the adhesive layers or agent reservoir layers in the device of Theeuwes et al. do not contain the same components as in the present invention. Namely although fentanyl as an active ingredient, poly (methyl vinylether co-maleic anhydride) as an adhesive, and hydroxypropyl cellulose, hydroxypropyl methylcellulose and hydroxyethyl cellulose as hydrophilic polymers are disclosed in Theeuwes et al., as indicated by the Examiner, **a drug layer** which specifically contains **a combination** of methyl vinyl ether-maleic anhydride copolymer as an adhesive, and at least one substance selected from the group consisting of hydroxypropyl cellulose, hydroxypropyl methylcellulose and hydroxyethyl cellulose as a thickener, is not disclosed therein; nor are the effects according to the present invention (as discussed above and in the paragraph bridging pages 4-5 of the specification) disclosed in the reference, which are unexpected from the reference disclosure.

Thus, the Theeuwes et al. reference discloses thousands of drugs under the heading BIOLOGICALLY ACTIVE AGENTS in columns 6-8, from among which fentanyl must be specifically selected in accordance with the present invention; thousands of polymers under the heading AGENT RESERVOIRS in columns 10-11, from among which hydroxypropyl methylcellulose must be specifically selected in accordance with the present invention; and also a large number of adhesives under the ADHESIVE heading in columns 11-12, from among which methyl vinyl ether-maleic anhydride copolymer must be specifically selected in accordance with the present invention.

However, this picking and choosing of materials and then combining them in order to arrive at the present invention is itself evidence of **lack** of anticipation.

Thus, as the C.C.P.A. stated in *In re Arkley,* 172 U.S.P.Q. 524, at 526:

> It is to be noted that rejections under 35 U.S.C. 103 are proper where the subject matter claimed "is not **identically** disclosed or described" (emphasis by Court) in "the prior art," indicating that rejections under 35 U.S.C. 102 are proper only when the claimed subject matter <u>is</u> (emphasis by Court) identically disclosed or described in "the prior art." Thus, for the instant rejection under 35

> U.S.C. 102(e) to have been proper, the Flynn reference must clearly and unequivocally disclose the claimed compound or direct those skilled in the art to the compound **without any need for picking, choosing, and combining** (Court emphasized "any"; rest of emphasis added) various disclosures not directly related to each other by the teachings of the cited reference. Such picking and choosing may be entirely proper in the making of a 103, obviousness rejection, where the applicant must be afforded an opportunity to rebut with objective evidence any inference of obviousness which may arise from the **similarity** (emphasis by Court) of the subject matter which he claims to the prior art, but it has no place in the making of a 102, anticipation rejection.

Similarly, in *In re Brink*, 164 U.S.P.Q. 247, the C.C.P.A. stated, at page 249:

> Just as the ambiguous reference failed as an anticipation under 35 U.S.C. 102 in In re Hughes, supra, we do not see how a disclosure or combination of the disclosures **leaving one to rely on fortune in choosing** (emphasis added) the referred to material can function as an anticipation.

Thus, it is readily apparent that since one skilled in the art would have to pick and choose from among the thousands of biologically active agents, agent reservoirs and adhesives disclosed in Theewes et al. those materials which would satisfy the presently claimed invention (fentanyl as a biologically active agent, hydroxypropyl methylcellulose as a polymer for the agent reservoir, and methyl vinyl ether-maleic anhydride copolymer as an adhesive), and then combine the materials in the manner required by the present invention, the reference does **not** constitute an **anticipation** of the invention.

That is, the arrangement or combination of the particular materials required in the present invention must be disclosed in Theewes et al. if the reference is to constitute an anticipation of the invention. In this regard, as the C.A.F.C. stated in *Connell v. Sears, Roebuck & Co.*, 220 U.S.P.Q. 193, at 198:

> Anticipation requires the presence in a single prior art disclosure of all elements of a claimed invention **arranged as in the claim.** [Emphasis added.] Soundscriber Corp. v. U.S., 360 F. 2d 954, 960, 148 U.S.P.Q. 298, 301 (Ct. Cl. 1966). A prior art disclosure that "almost" meets that standard may render the claim invalid under §103; it does not "anticipate".

Similarly, attention is directed to the decision of the Court of Appeals, 9th Circuit in **Jones v. Vefo Inc.**, 204 U.S.P.Q. 535, wherein at page 537 the Court stated that:

> Unless all of the same elements are found in exactly the same situation and **united in the same way** (emphasis added) to perform the identical function in a single prior art reference there is no anticipation.

For these reasons, Applicants take the position that the subject matter of claim 1 is not anticipated by the Theeuwes et al. reference.

The rejection of claims 1 and 2 under 35 U.S.C. §103(a) as being unpatentable over Yamaguchi et al. (US '877) in view of Inoue et al. (US '470) is respectfully traversed.

The Yamaguchi et al. reference relates to a percutaneously administrable patch drug preparation which can maintain the stability of a drug contained in the preparation during storage thereof by effectively inhibiting the drug from leaking and evaporation from the preparation. See column 1, lines 10-15. One of its objects is to provide a percutaneous patch drug preparation which can stably preserve therein an initial designed amount of a drug without loss thereof until the preparation is administered to a patient. See column 2, lines 44-47. Therefore, the object of the reference is different from that of the present invention.

The percutaneous or permucosal patch of Yamaguchi et al. is one consisting of (1) a backing layer impermeable to a drug component, (2) a drug storage layer containing the drug component which is situated under the central portion of the backing layer, (3) a protective film impermeable to the drug component, which has notches and is situated under the drug storage layer and the peripheral portion of the backing layer, (4) a pressure-sensitive adhesive layer which is situated under the protective film and (5) a releasable liner layer which is situated under the pressure-sensitive adhesive layer and is impermeable to the drug component. See Abstract and column 2, line 59 to column 3, line 5. The drug storage layer of Yamaguchi et al. contains generally 0 to 40% by wt. of a solvent selected from ethanol and ethanol-water, and further an additive such as viscosity-enhancing agents such as cellulose acetate and methyl cellulose; solubilizers or solubilizer assistants such as crotamiton and ethylene glycol; emulsifires, absorbefacients; or torpents. See column 4, lines 33-55. As mentioned above, the drug storage layer of Yamaguchi et al. basically contains a base consisting of a solvent selected from ethanol and ethanol-water, and does not itself exhibit adhesive power to the skin.

On the other hand, the drug (storage) layer of the present invention itself has adhesive power to the applied region.

Furthermore, the patch of present invention does not require a protective film impermeable to the drug component, which has notches under (on) the drug storage layer.

Therefore, the Yamaguchi et al. reference is completely different from the present invention in object and components, respectively.

The Inoue et al. reference relates to an oral bandage that can be adhered to the oral mucosa to prevent a drug administered to the oral mucosa from running out and to cover or protect the affected part of the oral mucosa, and a process for preparation thereof. See Abstract and column 1, lines 5 to 10.

The oral bandage of this reference is one comprising an adhesive film or a composite of such an adhesive film and soft film support, the adhesive film comprising a mixture of a polycarboxylic acid and/or a polycarboxylic acid anhydride and a vinyl acetate polymer in a compatible state. See column 2, lines 24-31. The reference is based on finding that polycarboxylic acids and polyvinyl acetate are compatible with each other, and mixing of these two components in a compatible state substantially realizes water-insolubilization of the polycarboxylic acids without impairing the strong adhesion upon water absorption. See column 2, lines 60-65. Furthermore, it was found that incorporation of a basic substance capable of neutralizing the polycarboxylic acids into the above-described compatible mixture can further relieve the irritation on the injured part of the oral mucosa. See column 3, lines 3-7.

The soft films comprising a compatible mixture of the polycarboxylic acids and polyvinyl acetate according to Inoue et al. do not show adhesion in a dry state, but come to exhibit strong adhesion upon water absorption. Such a characteristic can first be manifested when the polycarboxylic acid and polyvinyl acetate are in a compatible state, not when they are not in a compatible state. See column 3, lines 23-32.

In Inoue et al., as indicated by the Examiner, as examples of polycarboxylic acids, maleic anhydride polymers and copolymers such as copolymers of maleic anhydride and methylvinyl ether are illustrated. See column 6, lines 19-21.

However, the present invention provides a patch for the mucous membrane of an oral cavity which is sufficiently adhesive to the mucosa of the oral cavity by water, and is easily torn off when unnecessary, without the necessity of using vinyl acetate copolymer (polyvinyl

acetate), by admixing methyvinyl ether-maleic anhydride copolymer (e.g. 5-90 wt/%) as an adhesive, a substance selected from hydroxypropyl cellulose, hydroxypropylmethyl cellulose and hydroxyethyl cellulose as a thickener (e.g. 0.2-80 wt/%) in a drug layer, and therefore, the present invention is completely different from Inoue et al. in object and constitution, especially in point of not requiring a compatible mixture of the polycarboxylic acids and polyvinyl acetate. As such, Inoue et al. do not disclose using methyl vinyl ether-maleic anhydrate copolymer alone as an adhesive agent in an oral bandage. See column 14, Example 3, and column 16, Example 6. Although the Examiner indicates in the Office Action at page 8, that Inoue et al. disclose an adhesive film comprising a methyl vinyl ethermaleic anhydride copolymer (column 5, lines 33-48, etc.), the copolymer is illustrated as one component for forming a compatible state with another substance (polyvinyl acetate), and the copolymer is not solely meant to be used as an adhesive agent, as explained above.

Thus, Inoue et al. do not disclose a methyl vinyl ether-maleic anhydride copolymer as an adhesive agent.

Furthermore, as indicated above, the drug storage layer of the Yamaguchi et al. reference does not contain any adhesive agent. Therefore, even if this reference were combined with Inoue et al. in the manner suggested by the Examiner, the resultant combination would still not be the same as, or suggest, the presently claimed invention.

The rejection of claims 3 and 5 under 35 U.S.C. §103(a) as being unpatentable over Yamaguchi et al. in view of Inoue et al. and further in view of Miller, II et al. (US '551) is respectfully traversed.

The comments set forth above concerning the Yamaguchi et al. and Inoue et al. references are equally applicable to this rejection, it being noted that claims 3 and 5 are directly or indirectly dependent on claim 1.

The Miller II et al. reference relates to fentanyl suspension-based, silicone pressure sensitive adhesive formulations and their use in making devices for improved transdermal delivery of fentanyl. See Abstract. The reference is completely different in constitution and object from the present invention, which is intended to administer to an oral cavity, and in the patches of the present invention wherein fentanyl suspension-based, silicone pressure sensitive adhesive formulations need not be used.

The rejection of claim 4 under 35 U.S.C. §103(a) as being unpatentable over Yamaguchi et al. in view of Inoue et al. and further in view of Mizota et al. (EP '199) is respectfully traversed.

The comments set forth above concerning the Yamaguchi et al. and Inoue et al. references are equally applicable to this rejection, it being noted that claim 4 is dependent on claim 1.

The Mizota et al. reference relates to a patch comprising a laminate having an expansible support and an adhesive layer laminated on the support; and a release sheet, attached onto the adhesive layer, having perforations formed with a predetermined interval; wherein the laminate when formed into a test piece having a longer side of 20cm and a shorter side of 5cm exhibits a load of 0.98 to 14.71 N/5cm in both longer and shorter side directions at the time of 50% elongation, and a 50% elongation recovery ratio of 50 to 95% in both longer and shorter side directions. See Abstract, claim 1, etc.

The object of Mizota et al. is to provide a patch which can be applied beautifully and reliably in a short time when carrying out an operation of peeling a release sheet and an operation of applying the patch to an aimed part at the same time while being hard to peel off even when attached to a joint, a face, or the like for a long period of time. See paragraph [0006].

Mizota et al. do not disclose using a combination of methyl vinyl ether-maleic anhydride copolymer and at least one substance selected from the group consisting of hydroxypropyl cellulose, hydroxypropyl methylcellulose and hydroxyethyl cellulose in an adhesive layer.

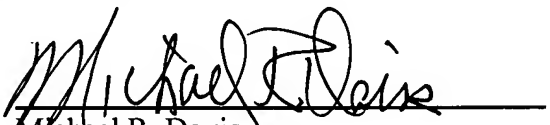
Therefore, even if this reference were combined with Yamaguchi et al. and Inoue et al. in the manner suggested by the Examiner, the resultant combination would still not be the same as, or suggest, the presently claimed invention.

Attention is also directed to new claim 6, which defines the drug layer in "consists of" language, thus excluding the other components of the references in the drug layer as discussed above. Applicants take the position that the references fail to disclose or suggest a patch having a drug layer containing only the components as recited in new claim 6.

Therefore, in view of the foregoing amendments and remarks, it is submitted that each of the grounds of objection and rejection set forth by the Examiner has been overcome, and that the application is in condition for allowance. Such allowance is solicited.

Respectfully submitted,

Katsumi IHARA et al.

By: 

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